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# Novel *FLNC* variants in pediatric cardiomyopathy: an insight into disease mechanisms

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**Abstract**

**Background** *FLNC* gene variants have predominantly been reported in adult populations with cardiomyopathies, and early-onset cases are less common. The genotype–phenotype relationship indicates that dilated cardiomyopathy (DCM) is often associated with *FLNC* truncating variants.

**Methods** We conducted a comprehensive genetic analysis using next generation sequencing (NGS) to identify *FLNC* variants in patients with cardiovascular conditions. Detailed phenotypic and variant analyses were performed to characterize the clinical features and genetic alterations. Minigene assays and structural modeling were used to investigate the pathogenicity caused by the identified variants.

**Results** In a cohort of 58 patients, novel heterozygous *FLNC* variants, c.3962A > T (p.Glu1321Val) and c.7543C > T (p.Leu2515Phe), were identified in patients presenting with dilated and mixed restrictive/hypertrophic cardiomyopathies, respectively. The c.3962A > T variant disrupted normal splicing, as demonstrated through the splicing prediction tool and minigene studies, further emphasizing its pathogenic potential.

**Conclusion** For missense variants of *FLNC* in patients with DCM, the splicing effect of the variant should be carefully checked. Early detection and intervention are crucial given the high risk of sudden cardiac death and severe cardiac complications.

**Keywords** *FLNC* variant, Cardiomyopathies, Early-onset, Splicing defects

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## Introduction

The *FLNC* gene, predominantly expressed in skeletal and cardiac muscle tissues, encodes filamin C (FLNC), a member of the filamin family of actin-binding proteins [1, 2]. The FLNC protein is localized within the Z-discs and intercalated discs, where it cross-links actin rods to other proteins of the fascia adherens junction, playing a pivotal role in maintaining the structural integrity and mechanotransduction of sarcomeres in cardiac and skeletal muscles [3]. Like its counterparts in the filamin family, FLNC serves a structural role featuring an actin-binding domain (ABD) that is constituted by a pair of calponin homology (CH) regions. This protein also encompasses 24 immunoglobulin-like (Ig-like) domains, which are further categorized into two subdomains known as ROD1

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and ROD2, alongside a dimerization domain located at the C-terminus [4]. It interacts with a multitude of proteins implicated in cardiomyopathy, including calpain, dystrophin, Cypher, and actin [5]. Variants in the *FLNC* gene not only correlate with myopathies but are also linked to a spectrum of inherited cardiomyopathies, as well as arrhythmias without overt structural heart disease. These conditions predominantly manifest as various patterns of functional impairment and structural abnormalities in the heart, often leading to severe morbidity and mortality [6–9]. *FLNC*-related inherited cardiomyopathies mainly include dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ACM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM) [10, 11].

*FLNC* variants have predominantly been reported in adult populations with cardiomyopathies, with an average age of onset of 39.7 ± 14.5 years for *FLNC*-DCM and a mean age of onset of 35.9 ± 14.8 years for HCM in *FLNC* carriers [12–14]. Truncating *FLNC* variants are associated with a high risk of dilative and arrhythmic cardiomyopathies, characterized by left ventricular dysfunction, fibrosis, ventricular arrhythmias, and sudden cardiac death (SCD) [15]. Our study reports novel missense variants in *FLNC* associated with pediatric cases. One missense variant leading to a frameshift and premature stop codon has been confirmed through genetic analysis in children presenting with DCM, while another missense variant is associated with a complex phenotype combining restrictive and hypertrophic cardiomyopathy.

## Materials and methods

### Study cohort

A total of 58 unrelated pediatric patients with cardiomyopathies, arrhythmias, and myocarditis were evaluated between 2018 and 2023 at our hospital. These patients underwent next-generation sequencing (NGS) using whole-exome sequencing (WES), trio-WES, or targeted exome sequencing of utilized a custom panel targeting around 5000 genes implicated in human genetic diseases.

### NGS

Genomic DNA was extracted from blood samples of probands and their parents. Sequencing was performed on an Illumina Novaseq 6000 after capturing with the IDT xGen Exome V2 kit. Raw sequence data were filtered and aligned to the UCSC hg19 reference genome using Sentieon software, achieving > 99% gene coverage at an average depth > 150X.

### Bioinformatics analysis and variant verification

Variants were annotated against databases (dbSNP, HapMap, 1000 Genomes, OMIM, gnomAD) and classified according to ACMG guidelines [16] using predictive algorithms (REVEL, PolyPhen-2, SIFT, MutationTaster). Candidate variants were confirmed by Sanger sequencing with custom primers designed by Primer Premier v5.0. Purified PCR products were sequenced bidirectionally on an ABI Prism 3730 automated sequencer.

### Conservation and functional analysis

Homology analysis was conducted with DNAMAN, and the splicing impact of the variants was predicted using Mobidetails (https://mobidetails.iurc.montp.inserm.f r/MD/genes). Structural modeling of FLNC proteins was done with SWISS-MODEL, visualized with PyMOL, and secondary structure predictions obtained with HNN (https://npsa-prabi.ibcp.fr/cgi-bin/npsa_automat.pl?page=/NPSA/npsa_hnn.htm l).

### Minigene splicing assay

To evaluate the specific impact of the c.3962A > T variant predicted to affect splicing by Mobidetails, a minigene assay was performed. The minigene construct encompassed exons 21, 22, and 23 along with their intervening introns from the *FLNC* gene. These regions were amplified from control genomic DNA via nested PCR using two primer pairs: 5′-GGGGCCCTACAAGGT GGATA-3′ and 5′-CCTCCCTTGTCTTCCCTGAG -3′; 5′-CCACCTGCCTTGGAGACAAC-3′ and 5′-CCA GTGAGTGAGGATGAGGG-3′. The resulting amplicons were cloned into the pcDNA3.1 vector (Invitrogen, Carlsbad, USA), and the wild-type construct was validated by Sanger sequencing. Mutant plasmids were generated by replacing the relevant segments with those produced by site-directed mutagenesis primers: BamHI-F (5′-GCT CGGATCCATGGT CTGTGCTTATGGCCCGGG-3′) and XhoI-R (5′-TAGACTCGAGCCTGGTCTCCA CAG TGAATCG-3′). The integrity of the mutant plasmid was also confirmed by Sanger sequencing. Selected recombinant plasmids were transiently transfected into HeLa and HEK293T cell lines using Lipofectamine 3000 (Invitrogen, Carlsbad, USA) as per the manufacturer's protocol. After 48 h of incubation, total RNA was isolated and reverse transcription PCR (RT-PCR) was performed using the primer pair: F (5′-GCTCGGATCCATGGT CTGTGCTTATGGCCCGGG-3′) and R (5′-TAGAAG GCA CAGTCGAGG-3′). Agarose gel electrophoresis was used to analyze the PCR products, and the splicing isoforms were identified by Sanger sequencing (Supplementary Material 1).

**Table 1** Clinical characteristics of the patients

| | **Patient 1** | **Patient 2** |
|---|---|---|
| Age at onset | 3y5m | 3y1m |
| Gender | Female | Female |
| Clinical features | Cardiac murmur | Cyanosis during strenuous activity; Frequent common colds; Poor endurance; Short stature |
| Pathology | Dilated cardiomyopathy | Restrictive and hypertrophic cardiomyopathy |
| Cardiac ultrasound | EF:39%; Increased left ventricular end-diastolic diameter (35 mm); interventricular septum bulging; Decreased left ventricular wall motion; Increased LVEDV (Z-score = 4.014) | EF:67%; Bilateral atrial enlargement (left: 35 mm, right: 49 mm); Thickened interventricular septum (6.27 mm) and right ventricular walls (4.62 mm); Pulmonary hypertension (67 mmHg); Mitral and tricuspid valve regurgitation; Minimal pericardial effusion |
| Electrocardiogram | Sinus arrhythmia; Preexcitation (type B) | Sinus arrhythmia; Bilateral atrial abnormalities; Occasional premature atrial contractions; First-degree atrioventricular block; Left ventricular high voltage; ST-T changes |
| Hepatic ultrasound | Normal | Hepatomegaly |
| Chest radiological findings | Normal-sized heart; Increased pulmonary markings | Cardiomegaly; Pneumonia, lung consolidation, pleural effusion |
| BNP (reference, 0-100 pg/ml) | < 10 | 2776.3↑ |
| Blood routine test | | |
| WBC (reference, 4.4- 11.9 × $10^9$/L) | 11.16 | 6.89 |
| ANC (reference, 1.2- 7.0 × $10^9$/L) | 7.18↑ | 3.27 |
| Hb (reference, 112–149 g/L) | 120 | 109↓ |
| CRP (reference, 0–10 mg/L) | 19.1↑ | 10.5↑ |
| ESR (reference, 0–20 mm/h) | 17 | 56↑ |

y, years; m, months; EF, ejection fraction; LVEDV, Left ventricular end-diastolic volume; BNP,B-type Natriuretic Peptide; WBC, white blood cells; ANC, absolute neutrophil count; HB, hemoglobin; CRP,C-reactive protein; ESR, erythrocyte sedimentation rate

## Results

In our cohort, 2 (3.4%) patients (Table 1) were found to carry disease-related FLNC variants. Other common variants included MYBP3 (4, 6.9%), GAA (3, 5.2%), and TTN (2, 3.4%) (Supplementary Material 2).

### Patient 1 with *FLNC* variant

A 3-year-5-month-old female was referred following the detection of a cardiac murmur and recent onset of fever. Initial examination revealed a grade 3/6 systolic murmur audible along the left sternal border at the second intercostal space, with normotensive blood pressure and heart rate. Echocardiography (Fig. 1) demonstrated a reduced ejection fraction (EF), dilated and hypokinetic left ventricle, and bulging of the basal interventricular septum towards the right ventricular side. Based on the left ventricular end-diastolic volume (LVEDV), the Z-score was greater than 2, indicating a significant deviation from the normal range for age. Holter monitoring revealed sinus arrhythmia and B-type pre-excitation. Chest X-ray showed increased pulmonary markings without cardiomegaly. Blood tests suggested an inflammatory response and slightly low thyroid hormone levels. Cardiac enzymes, B-type natriuretic peptide (BNP), high-sensitivity troponin (hsTnI), liver and renal function tests, coagulation profile, immunoglobulins, electrolytes, and ultrasound of the liver and spleen were all within normal limits. She was treated with milrinone, digoxin, diuretics, and anti-infective therapy. After resolving the infection, her EF improved to 51% and she was discharged.

Upon discharge, the patient was prescribed oral hydrochlorothiazide, spironolactone, and digoxin. At the 6-month follow-up, her EF had stabilized at over 50%. Subsequently, the treatment regimen was adjusted to include oral propafenone for 3 months. At the 12-month follow-up, a repeat echocardiogram demonstrated further improvement in cardiac function, with the EF ranging between 60 and 70%. While the left ventricular dilation and hypokinesis showed some improvement, the overall clinical status of the patient remained stable, and she continued to show no signs of recurrent infection or worsening cardiac symptoms.

### Patient 2 with *FLNC* variant

A 3-year-1-month-old girl was referred for cardiac evaluation after presenting with fever, cough, and exertional cyanosis. Chest radiography revealed cardiac silhouette enlargement. She has a history of frequent colds, poor endurance, and reduced physical activity, although she has achieved standard developmental motor milestones.

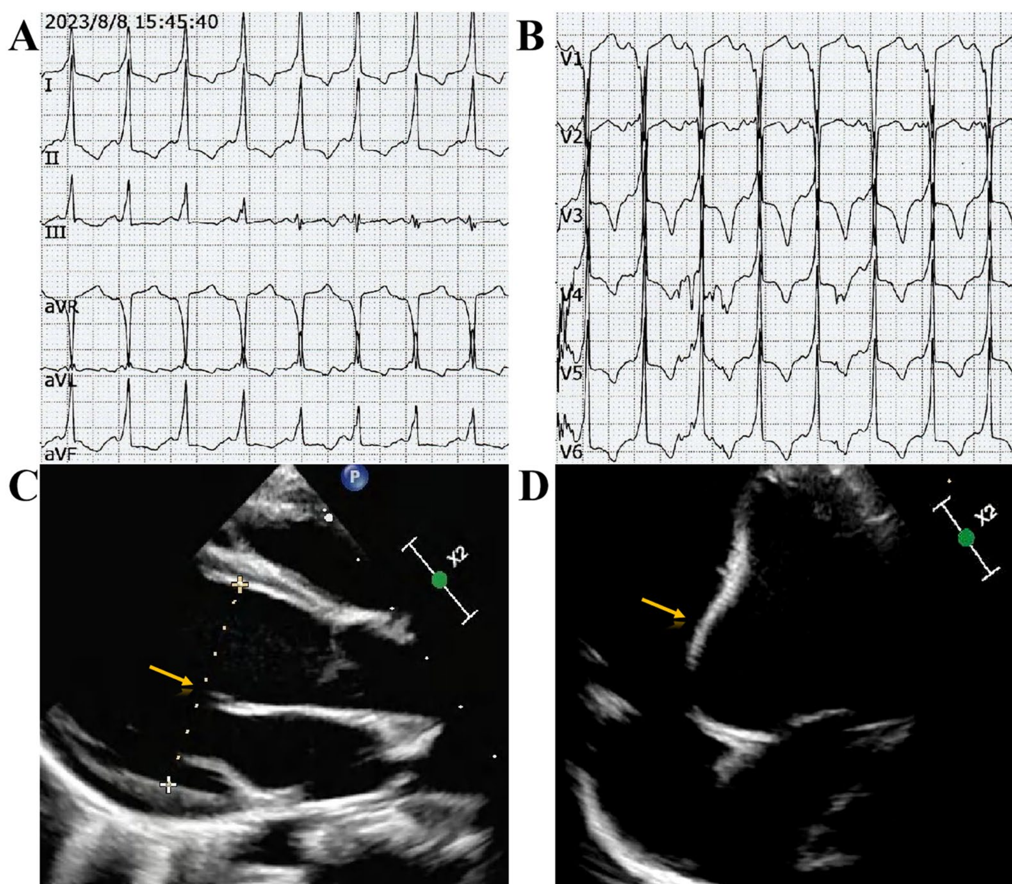


**Fig. 1** Cardiac evaluation of two patients. **A**-**B**: Patient 1's Holter; **C**: Left ventricle dilation in Patient 1; **D**: Septal bulge in Patient 1; **E**–**F**: Patient 2's Holter; **G**: Right atrium enlargement in Patient 2; **H**: Thickened septum in Patient 2

At presentation, her blood pressure was 107/73 mmHg, height was 89 cm (3rd to 10th percentile), and weight was 13 kg (10th to 25th percentile). Coarse breath sounds and scattered crackles were noted bilaterally. Enlargement of the liver was palpable below the costal margin. Cardiac examinations were unremarkable. Echocardiography disclosed a preserved EF with dilated atria, thickened interventricular septum and right ventricular walls, moderate pulmonary hypertension, valvular regurgitations, and a small pericardial effusion. Hepatic ultrasonography suggested congestion with hepatomegaly, altered venous structures, and enlarged portal lymph nodes. Holter monitoring indicated sinus arrhythmia, atrial abnormalities, and signs of myocardial ischemia. Laboratory tests revealed elevated BNP levels, prolonged prothrombin time, increased D-dimer, and evidence of inflammation and infection. CT thorax confirmed pulmonary involvement, pleural effusion, and cardiac silhouette enlargement. No significant deviations were observed in additional biochemical markers or imaging assessments. Upon admission, the patient was treated with hydrochlorothiazide, spironolactone, levocarnitine, and antimicrobial therapy for eight days, resulting in clinical improvement and discharge.

Upon discharge, the patient was prescribed oral spironolactone and hydrochlorothiazide, and she continued to take antibiotics for 5 days as part of her discharge regimen. At the 2-month follow-up post-discharge, the patient exhibited reduced cyanosis, and a repeat echocardiogram demonstrated amelioration of pulmonary hypertension, with other findings consistent with the previous assessment. Since the 2-month follow-up, the patient has not undergone further echocardiographic or electrocardiographic evaluations. However, her clinical symptoms have remained stable, and her activity tolerance is satisfactory. There have been no reports of fever, infection, or cyanosis over the subsequent 5 months. The parents have continued to administer the prescribed medications as directed.

Both patients are the first-born children of their respective parents and have no siblings. Neither patient has a family history of cardiomyopathy or myocarditis

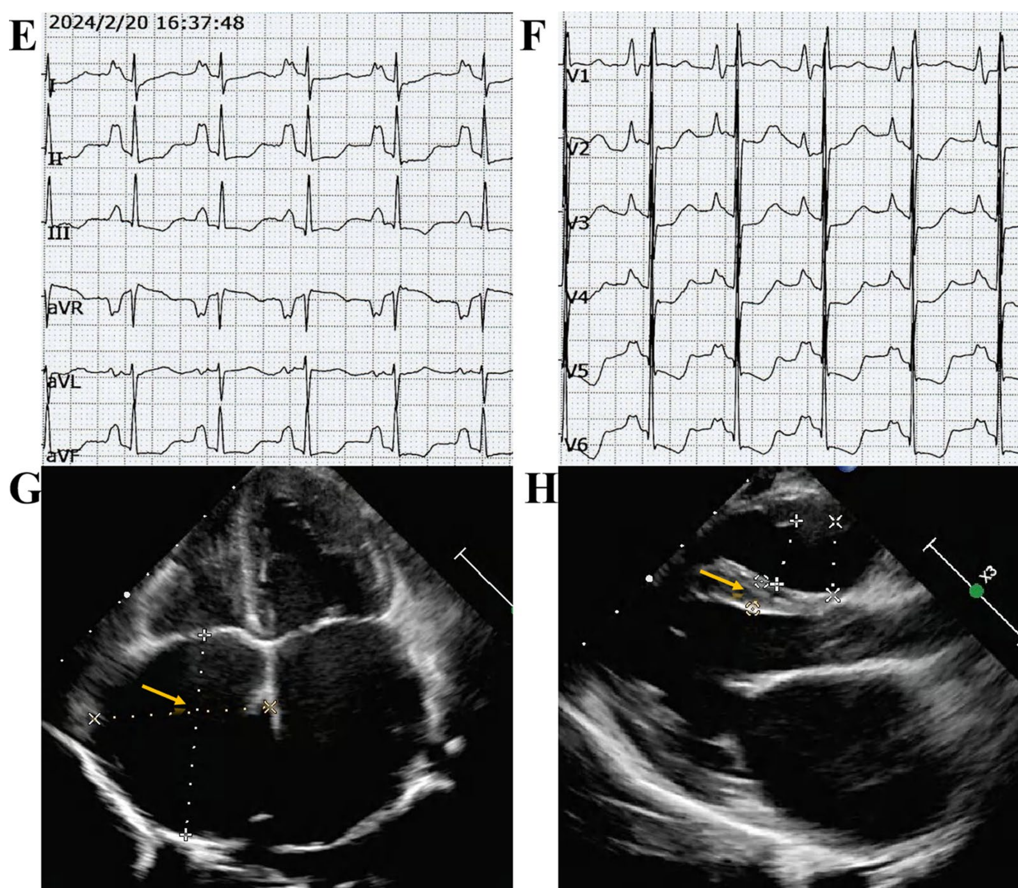


**Fig. 1** continued

extending up to three generations. Both families are of East Asian descent from China.

**Genetic findings**

The de novo heterozygous variations c.3962A > T (p.Glu1321Val) and c.7543C > T (p.Leu2515Phe) in the *FLNC* gene were respectively identified in the index patients (Fig. 2). The c.3962A > T variant leads to the substitution of glutamic acid with valine at position 1321 of the encoded protein, while the c.7543C > T variant results in the replacement of leucine with phenylalanine at position 2515. According to the ACMG guidelines, both variants were classified as likely pathogenic (PS2 + PM2_Supporting + PP3): 1) the variants were determined to be de novo; 2) The variants were not present in the gnomAD database of normal population; 3) Multiple bioinformatic tools predicted the variants to be deleterious.

**Bioinformatics analysis**

Conservation analysis with DNAMAN shows strong preservation at FLNC protein positions 1321 (Glu) and 2515 (Leu), with PhyloP scores of 4.854 and 3.35, respectively (Fig. S1). The p.Glu1321Val variant poses a high risk of splicing disruption, supported by an MPA score of 10 and spliceAI predictions suggesting likely alterations in nearby splice donor sites (Fig. S2). Structural modeling, guided by minigene assays and referencing PDB ID Q8BTM8.1.A, suggests that p.Glu1321Val, located within the ROD1 domain, may disrupt this domain, leading to protein truncation. While p.Leu2515Phe, situated in the ROD2 domain, does not significantly affect the overall 3D structure, secondary structure prediction indicates a transition from a random coil to an alpha helix at position 2530 (Fig. S2).

**Splicing study of *FLNC* c.3962A > T by minigene assay**

The outcomes of the minigene splicing assay reveal that the c.3962A > T (p.Glu1321Val) variant disrupts canonical splicing, as evidenced by a recurrent 4 base pair deletion at the right flank of Exon 22 across independent cellular analyses. At the molecular level, this deletion is represented as c.3961_3964del (p.Glu1321Alafs*23) in the cDNA sequence, leading to a frameshift variant and the incorporation of a premature stop codon within Exon

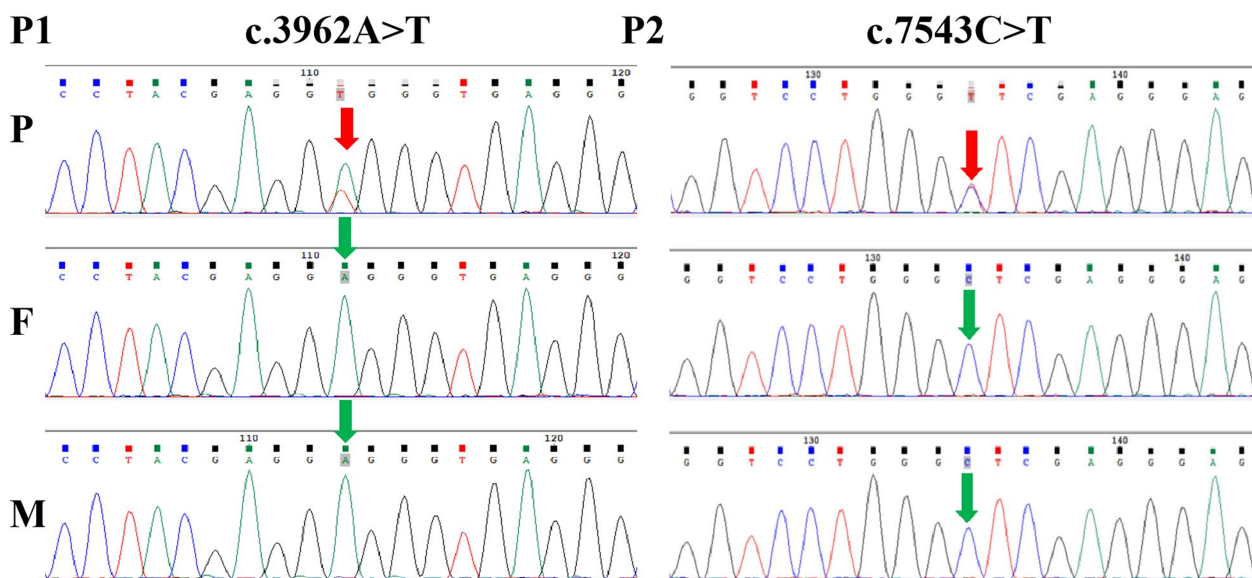


**Fig. 2** Sanger sequencing reveals de novo variants c.3962A > T (p.Glu1321Val) in Patient 1 and c.7543C > T (p.Leu2515Phe) in Patient 2

23. This de novo variant has not been previously reported and results in a shortened protein isoform of putative 1342 amino acids, diverging significantly from the wild-type protein structure (Fig. 3).

At the molecular level, this deletion is represented as c.3961_3964del in the cDNA sequence, leading to a frameshift variant and the incorporation of a premature stop codon (p.Glu1321Alafs*23) within Exon 23. Consequently, a shortened protein isoform of putative 1342 amino acids may be produced, diverging significantly from the wild-type protein structure (Fig. 3).

## Discussion

*FLNC* variants have been identified in 2.8% of Italian pediatric patients with cardiomyopathies, arrhythmias, and congenital heart defects (CHDs) [17]. In our study, 3.4% of Chinese pediatric patients with cardiomyopathies, arrhythmias, and myocarditis (excluding CHDs) were found to harbor *FLNC* variants. Despite the comparable prevalence rates, the higher incidence of CHDs in the Chinese population may contribute to a potentially lower overall prevalence of *FLNC*-related cardiac conditions in Chinese pediatric patients relative to their Italian counterparts. Both of our patients presented with an infectious context, which raises the possibility of myocarditis as a contributing factor. In patient 1, the EF improved significantly after treating the infection, suggesting that the initial reduction in EF might have been partly due to myocarditis. However, the persistent left ventricular dysfunction and other structural changes observed on echocardiography, such as dilatation and hypokinesis, indicate a more complex underlying condition. Additionally, it is noteworthy that *FLNC* gene truncating variants have been reported to lead to adult myocarditis [18]. Follow-up studies have shown that myocarditis can be the initial manifestation of ACM caused by *FLNC* truncating variants. This finding underscores the importance of considering myocarditis as a potential early indicator of *FLNC*-related cardiomyopathy, even in pediatric patients.

Recent studies have identified genotype–phenotype correlations in *FLNC* variants, particularly in both pediatric and adult early-onset cardiomyopathy. De novo variants in *FLNC* have been reported to be potentially associated with more severe phenotypes [13]. Pathogenic variants in *FLNC* causing cardiomyopathy are mostly localized to the ROD1 and ROD2 domains, recognized as hotspots [19]. The ROD2 domain is implicated in cell signaling, and missense variants here correlate with HCM, clustering in this area to suggest a critical role in the development of the HCM phenotype. Conversely, variants in the ROD1 domain are linked to a variety of phenotypes, including DCM, RCM, and arrhythmogenic right ventricular cardiomyopathy (ARVC) [14]. Missense variants in the ROD1 and ROD2 domains are more prevalent in HCM patients, while in RCM patients, variants tend to concentrate on specific residues in the ROD2 domain, such as positions 2297 and 2298, and in left ventricular non-compaction (LVNC) patients, observed variants locate in the ROD2 domain [20]. In our study, two cases of pediatric early-onset cardiomyopathy were confirmed to harbor spontaneous missense variants in

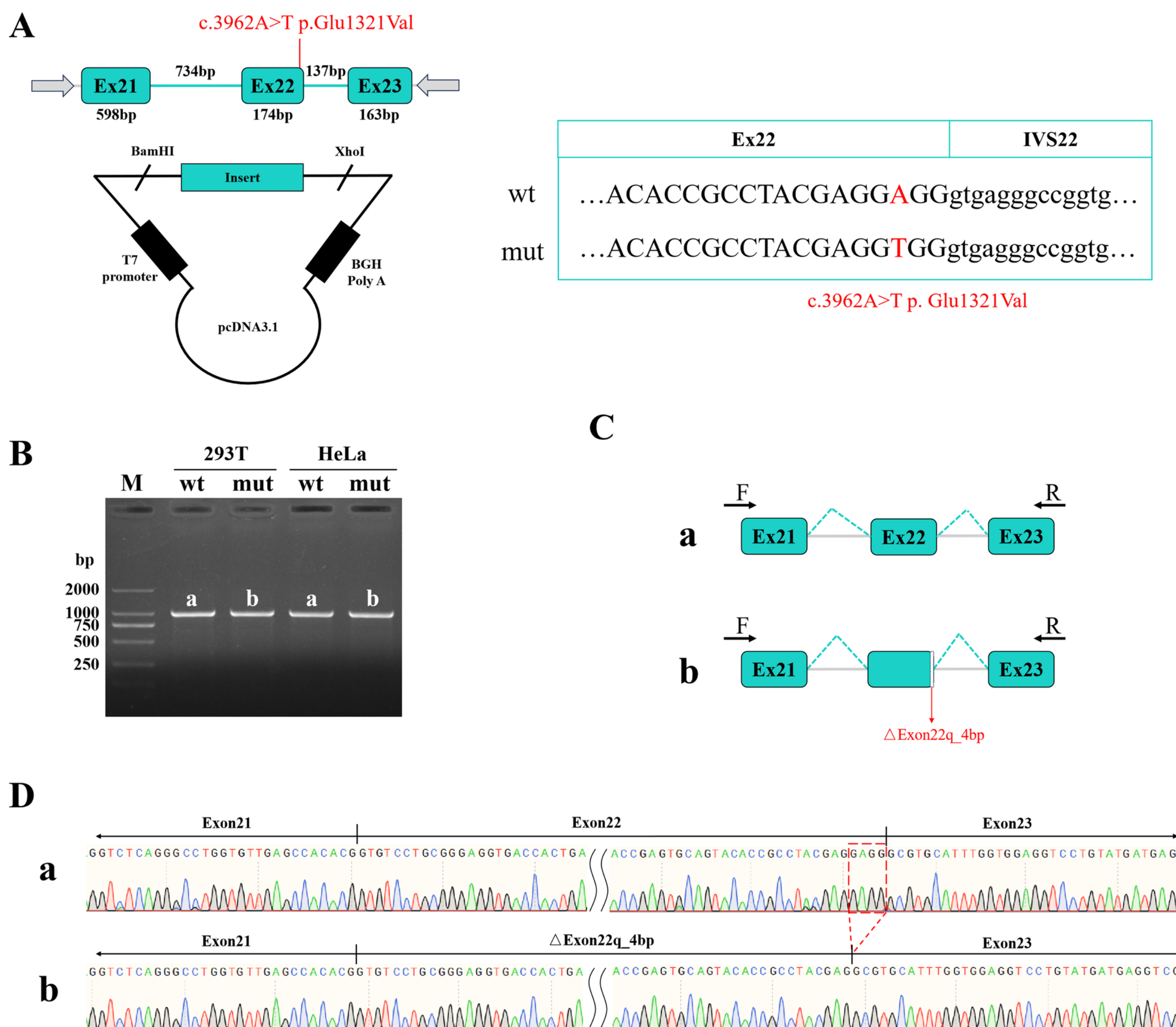


**Fig. 3** **A**: Construction strategy diagram of the minigene; **B**: Agarose gel electrophoresis image from RT-PCR transcript analysis; bands are labeled 'a' and 'b' in both HeLa and 293 T cells; **C**: Schematic illustration of the minigene splicing pattern; **D**: Sequencing results corresponding to the spliced bands depicted

*FLNC* located within the ROD1 or ROD2 functional domains. Specifically, the c.3962A > T variant, associated with DCM, underwent comprehensive analysis and validation, providing robust evidence that it is a truncating variant altering protein length and contributing to DCM pathogenesis. Specifically, the c.3962A > T variant, associated with DCM, underwent comprehensive analysis and validation, providing robust evidence that it is a truncating variant altering protein length and contributing to DCM pathogenesis. The c.7543C > T variant in the ROD2 domain, potentially disrupting the secondary structure of FLNC, was associated with a patient displaying characteristics of both restrictive and hypertrophic cardiomyopathy. The specific amino acid positions affected by these variants have not been previously reported as sites of pathogenic variants in cardiomyopathies. However, the surrounding regions of these residues have been associated with pathogenic variants in other studies, which suggests that alterations in these positions could have significant functional consequences [21, 22].

While rare, literature documents that variants in the *FLNC* gene can result in mixed cardiomyopathy phenotypes, combining features of both hypertrophic and restrictive conditions—a scenario similarly encountered in our findings. A report documented a 6-year-old girl with restrictive cardiomyopathy and septal

hypertrophy, where whole-exome sequencing revealed a novel heterozygous missense variant in *FLNC* [23]. Nathalie Gaudreault et al. described a novel *FLNC* variant (p.Ile1937Asn) that produced heterogeneous cardiomyopathy phenotypes in a large French-Canadian family, including one member with mixed hypertrophic-restrictive cardiomyopathy [24]. Our patient with the c.7543C > T variant exhibited prominent features of restrictive cardiomyopathy alongside significant septal and right ventricular hypertrophy, underscoring the complexity of *FLNC* gene variant involvement in cardiomyopathy pathogenesis. In light of previous experience and the complex phenotype associated with the *FLNC* gene in patient 2, comprehensive management strategies, including regular monitoring, pharmacological therapy, and timely intervention, are essential [25]. Considering the high risk of SCD and major ventricular arrhythmias (MVA) in patients with *FLNC* truncating variants, it is crucial to evaluate the need for an implantable cardioverter defibrillator (ICD) even in the absence of severe left ventricular dysfunction, especially in patients who present with ventricular arrhythmias [25]. Furthermore, early consideration of heart transplantation may be necessary due to the significantly lower transplant-free survival observed in children with restrictive cardiomyopathy and pathogenic variants [26].

## Conclusions

In summary, this work reinforces the importance of genetic testing as an indispensable tool in diagnosing pediatric heart diseases, particularly those of unknown etiology. Additionally, our findings highlight the importance of carefully checking the splicing effect of *FLNC* missense variants in patients with DCM. This approach can help identify the underlying genetic causes and guide appropriate clinical management, thereby improving patient outcomes.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40246-024-00683-9.

Supplementry Meterial 1

Supplementry Meterial 2

Supplementry Meterial 3: Fig. S1. Conservation analysis of p.Glu1321 and p.Leu2515 across multiple species

Supplementry Meterial 4: Fig. S2 A: Green indicates the conserved regions before and after the variant; cyan denotes the truncated region post-variant; yellow represents the calponin homology1 domain; red signifies the calponin homology2 domain; orange and blue depict the 24 immunoglobulindomains. B: Secondary structure analysis reveals a shift from random coil to alpha-helix at position 2530, triggered by the p.Leu2515Phe variant

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**Author contributions**
RD, XZ and YL conceived and designed this study. Experiments were conducted by HZ. Data were analyzed by RD and HZ. Clinical diagnosis of the patients was undertaken by GL and XZ. The paper was written by RD and BS.

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**Availability of data and materials**
The primary sequencing data documented in this article have been archived in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2021) hosted by the National Genomics Data Center (Nucleic Acids Res 2022), a division of the China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences (Accession No. GSA-Human: HRA007959). These data are freely accessible online at https://ngdc.cncb.ac.cn/gsa-human.

## Declarations

**Ethics Approval and Consent to participate**
Approval for this study was granted by the Institutional Review Board of the Children's Hospital Affiliated to Shandong University (Approval No. SDFE-IRB/P-2022015). Prior to enrollment, written informed consent was secured from the legal guardians of the participant for the inclusion in the study and the dissemination of associated data, images, and videos pertinent to the case report. To ensure confidentiality, all personal identifiers were removed from the patient's information prior to submission.

**Competing interests**
The authors affirm that they do not have any conflicts of interest that might influence the outcomes or interpretation of this research.

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